ELECTRONIC INFORMATION DISCLOSURE STATEMENT

Electronic Version v18

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Title of Invention	Topical Preparation and Method for Transdermal Delivery and Localization of Therapeutic Agents

Application Number: 10/709880 *10/709880*

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(3953599 or 4783450 or 4847250 or 4933184 or 4960771 or 4963367 or 5167616 or 5188837 or 5234957 or 5326566 or 5331000 or 5332576 or 5368860 or 5443829 or 5446070 or 5482965 or 5601838 or 5613958 or

5650398 or 5654337 or 5719197 or 5750141 or 5780051 or 5807568 or 5820877 or 5837289 or 5849737 or 5891463 or 5900249 or 5942241 or 5948389 or 5976547 or 5976566 or 5985317 or 5985860 or 5993836 or 5993849 or 6007843 or 6576791 or 6611706 or 6645980 or 6677332 or 6709706 or 6721603 or 6723345 or 3551554 or 4379792 or 6756052 or 20020004481 or 20020037319 or 20020052319 or 20020136788 or 20020168412 or 20020176892 or 20030012830 or 20030118651 or 20030161867 or 20040087520 or 20040126415 or 20040127531 or 20040142911 or 20040146590 or 20040151784).pn.

US Patent Documents

Note: Applicant is not required to submit a paper copy of cited US Patent Documents

init	Cite.No.	Patent No.	Date	Patentee	Kind	Class	Subclass
	1	3953599	1976-04-27	MacMillan et al.		514	304
	2	4783450	1988-11-08	Fawzi et al.		514	78
	3	4847250	1989-07-11	Alexander et al.		514	247
	4	4933184	1990-06-12	Tsuk		424	449
	5	4960771	1990-10-02	Rajadhyaksha		514	228.8
	6	4963367	1990-10-16	Ecanow		424	485
	7	5167616	1992-12-01	Haak et al.		604	20
	8	5188837	1993-02-23	Domb		424	450
	9	5234957	1993-08-10	Mantelle		514	772.6
	10	5326566	1994-07-05	Parab		424	401
	11	5331000	1994-07-19	Young et al.		514	570
	12	5332576	1994-07-26	Mantelle		424	443
	13	5368860	1994-11-29	Sunami et al.		424	448
	14	5443829	1995-08-22	Kensil et al.		424	765
	15	5446070	1995-08-29	Mantelle		514	772.6
	16	5482965	1996-01-09	Rajadhyaksha		514	452

	17	5601838	1997-02-11	Hind	424	443
	18	5613958	1997-03-25	Kochinke et al.	604	307
	19	5650398	1997-07-22	Kensil et al.	514	25
	20	5654337	1997-08-05	Roentsch et al.	514	570
	21	5719197	1998-02-17	Kanios et al.	514	772.6
	22	5750141	1998-05-12	Roberts et al.	424	449
	23	5780051	1998-07-14	Eswara et al	424	449
	24	5807568	1998-09-15	Cody et al	424	444
	25	5820877	1998-10-13	Yamaguchi et al.	424	449
	26	5837289	1998-11-17	Grasela et al.	424	484
	27	5849737	1998-12-15	Chaplan et al.	514	238.8
	28	5891463	1999-04-06	Bello et al	424	449
	29	5900249	1999-05-04	Smith	424	443
	30	5942241	1999-08-24	Chasin et al.	424	426
	31	5948389	1999-09-07	Stein	424	45
	32	5976547	1999-11-02	Archer et al	424	742
	33	5976566	1999-11-02	Samour et al.	424	449
	34	5985317	1999-11-16	Venkateshwaran et al.	424	449
	35	5985860	1999-08-31	Toppo	514	159
	36	5993836	1999-11-30	Castillo	424	401

	37	5993849	1999-11-30	Assmus et al.		424	449
	38	6007843	1999-12-28	Drizen et al.		424	488
	39	6576791	2003-06-10	Axt et al.	B1	564	157
	40	6611706	2003-08-26	Avrahami et al.	B2	604	20
	41	6645980	2003-11-11	Cuny et al.	B1	514	312
	42	6677332	2004-01-13	Cuny et al.	B1	514	212.02
	43	6709706	2004-03-23	Zhong et al.	B2	427	333
	44	6721603	2004-04-13	Zabara et al.	B2	607	46
	45	6723345	2004-04-20	Drizen et al.	B2	424	484
	46	3551554	1970-12-29	Herschler		424	9.4
	47	4379792	1983-04-12	Blaine		514	369
	48	6756052	2004-06-29	Koch et al.	B1	424	448

US Published Applications

Note: Applicant is not required to submit a paper copy of cited US Published Applications

init	Cite.No.	Pub. No.	Date	Applicant	Kind	Class	Subclass
	1	20020004481	2002-01-10	Cleland et al.	A1	514	12
	2	20020037319	2002-03-28	Drizen et al.	A1	424	488
	3	20020052319	2002-05-02	Pasternak et al.	A1	514	12

	4	20020136788	2002-08-31	Quezada	A1	424	742
	5	20020168412	2002-11-14	Drizen et al.	A1	424	488
	6	20020176892	2002-11-28	Drizen et al.	A1	424	488
	7	20030012830	2003-01-16	Small	A1	424	727
	8	20030118651	2003-06-26	Jampani	A1	424	473
	9	20030161867	2003-08-28	Lu et al.	A1	424	449
	10	20040087520	2004-05-06	Chowdhury et al.	A1	514	35
	11	20040126415	2004-07-01	Lu et al.	A1	424	449
	12	20040127531	2004-07-01	Lu et al.	A1	514	378
	13	20040142911	2004-07-22	Small	A1	514	159
	14	20040146590	2004-07-29	Iadarola	A1	424	760
	15	20040151784	2004-08-05	Varadhachary	A1	424	687

Remarks

Note: Remarks are not for responding to an office action.

Following is a "concise explanation of relevance" under 37 CFR 1.98(a)(3) and MPEP 609 A(3), for all of the references cited in this information disclosure. The U.S. Patent literature discloses many patent for enhancing the transdermal penetration of various medicating agents. Among these are the following: US 3,551,554 appears to be the basic background patent relating to DMSO as a penetration enhancer. US 4,783,450 appears to disclose a method of enhancing

penetration of a drug through the skin or other biological membranes using lecithin. US 4,963,367 appears to disclose use of polyerization to create compositions that facilitate drug transport. US 5,167,616 appears to disclose use of iontophoresis as a method of drug delivery across skin. US 5,443,829 appears to disclose to utilize "modified saponins" for enhancing the transport of pharmacologically active substances across mucous membranes. US 5,891,463; 5,985,317; 5,985,860 and 5,993,849 all appear to disclose the preparation of various adhesive patches for transdermal drug delivery. US 4,933,184 appears to disclose compositions and methods for enhancing the transdermal delivery of physiologically active agents, comprising a percutaneous transfer enhancing amount of menthol and a drug. US 5,188,837 appears to disclose a lipsophere for controlled delivery of active substances. In something of a departure from the above, US 6,611,706 and US 6,721,603 appear to disclose an alternative method of transporting drugs across skin, utilizing electrical current. US 6,721,603 also appears to disclose treating pain by application of a modulating electric signal to a selected nerve or nerve bundle, particularly by selective electrical stimulation of at least one of the trigeminal, glossopharyngeal, vagus and sympathetic nerves. Also in a somewhat differing approach, US 2004/0146590 appears to disclose selective ablation of pain sensing neurons, and in particular, requires "surgical" application of the VR-1 receptor agonist to the appropriate neuron, somewhat akin to a neurectomy or rhizotomy. US 5,780,051 pertains to nicotine withdrawal system. US 5,849,737 appears to disclose a means to relieve pain with minimal discussion of penetration mechanisms. US 3,953,599 appears to disclose generally, use of compositions to enhance penetration of scopolamine through the skin. US 4,379,792 appears to disclose a renal vasodilator together with an NSAID, the stated purpose of which is to enhance pharmacological activity by providing

the option of using NSAIDs in patients with impaired renal function. The primary route of administration is oral, and it is clear that this invention requires systemic absorption & distribution, even if administered topically. US 4,847,250 relates to pyroglutamic acid esters used as dermal penetration enhancers to achieve absorption of various non-pain drugs for systemic (not localized) effect. US 4,960,771 appears to disclose a composition or group of compositions designed to facilitate transport of drugs across the skin into the body. It both states and implies that this method would be for systemic distribution of drug thru the body. US 5,234,957 appears to disclose topical application of local anesthetic using a polyhydric alcohol, namely, polygalkeyene glycol, as the solvent. US 5,326,566 appears to disclose enhancing and/or controlling epidermal, dermal and transdermal penetration of topically applied pharmacologically active agents by use of dibutyl adipate, or a mixture of dibutyl adipate and isopropyl myristate. US 5,331,000 appears to disclose utilizing optically pure R(-) ketoprofen via oral ingestion, not over intact skin. US 5,332,576 appears to disclose an local anesthetic for topical application with a polyhydric alcohol, polygalkeyene glycol, as the solvent. US 5,368,860 appears to disclose patch technology utilized to facilitate topical use of local anesthetic. US 5,443,829 and 5,650,398 appear to disclose to utilize "modified saponins." US 5,446,070 appears along the lines of many patent to disclose topical application of a local anesthetic with a solvent. US 5,482,965 appears to disclose use of penetration enhancing agents or a physiologically acceptable salt thereof. US 5,601,838 appears to disclose a "patch" transdermal delivery system, namely, "The Lidoderm Patch." US 5,613,958 appears to disclose a "patch" device to facilitate and enhance topical absorption and transport of various drugs into the body, which are then picked up by the bloodstream and distributed for systemic effect. US 5,654,337

appears to disclose a chemical method to enhance uptake of various drugs topically from the skin, without and disclosure or suggestion to impede vascular uptake and dispersion from the site of action. US 5,719,197 appears to disclose use of an local anesthetic or NSAID plus a solvent. US 5,807,568 appears to disclose a method for optimizing the topical absorption & utilization of a particular NSAID, fluribprofen. US 5,820,877 appears to disclose preparation of a transdermal patch. US 5,837,289 appears to disclose the use of at least two separate penetration enhancers acting together to enhance medication penetration through the skin. US 5,900,249 appears to disclose various embodiments of a gel with pain-relieving effects, but does not address the fundamental issues of localized-versus-systemic effect, duration of action and synergy of components. US 5,942,241 appears to disclose utilizing local anesthetic(s) topically to relieve pain, however, approaches this issue by prolonging release of the drug rather than using vascular constriction to localize absorption following skin penetration. US 5,948 389 appears to disclose applying an opioid or local anesthetic to dissolved in an hyperosmolar solution. Duration of effect is not addressed, and there is no mention of a means to prolong effect at site of action. US 5,976,547 appears to disclose a topical over-the-counter & prescription strength analgesic and antiphlogistic blended compositions for reducing inflammation & providing relief from both peripheral & central pain as well as to a flexible therapeutic wrap for topical delivery of said blended compositions. There is no disclosure or suggestion of ingredients to facilitate transport of drugs through skin and localization of active drugs at target site. US 5,976,566 appears to disclose generally, utilizing NSAIDs topically to relieve pain. US 5,993,836 appears to disclose a specific mixture of two local anesthetics for topical application to block the pain of short needle procedures, for example, starting IVs in

children, and is unrelated to the treatment of chronic pain. US 6,007,843 appears to disclose a drug dispersed within a polymer matrix. The examples provided involve injection of the compound, not topical application. There is no mention of use of active substances to effect penetration thru the skin or maintenance of the active drug at the target site. US 6,576,791 appears to disclose creation of new compounds of local anesthetic drugs utilizing multi-binding ligands to affect long-acting local anesthetic effect. US 6,645,980 and 6,677,332 appear to disclose use of various analgesics as novel heterocyclic compounds for treatment of chronic pain, and as ligands for various receptors. This uses a polymeric carrier as and additive combined with active drug for delivery. US 6,709,706 appears to disclose a method for making a bicontinuous, conductive pressure-sensitive adhesive (PCA) such that the starting microemulsion has a convenient viscosity for coating, and such that only a single polymerization step is needed. This includes discovery of a class of thickening agents having a carboxyoxylic acid functionality that are compatible with the micro-emulsion and yet do not damage the properties of the final adhesive. US 6,723,345 appears to disclose the use of NSAIDs in polymer matrix with strong negative charge, or which are non-ionic. Matrix suspension facilitates controlled transmission through skin to achieve systemically significant drug blood levels. US 6,756,052 appears to disclose a penetration-enhancer which derives its efficacy from producing a local temperature increase in the skin and / or increases the circulation to facilitate topical absorption of drugs to be utilized systemically. US 2002/0004481 and 2002/0052319 appear to disclose using local anesthetics, opioids and NMDA receptor antagonists. Topical administration of the pharmaceutical composition is directed to cutaneous, mucosal, vaginal, rectal, ocular or nasal surfaces, which implies a systemic effect. US 2002/0136788 appears to disclose a therapeutic

oil composition for topical application to painful areas of the human body. US 2002/0037319; 2002/0168412; and 20020176892 appear to disclose topical gelled compositions to deliver analgesic and adjuvant drugs to a site of acute or chronic pain via topical application. They do not employ any form of localization. US 2003/0012830 appears to disclose topical compositions and methods to relieve pain, comprising an effective amount of acetone, a salicylate-based compound, and an emollient. In addition, these compositions further comprise one or more compounds including but not limited to, terpenes and essential oils. There is no limitation of systemic dispersal. US 2003/0118651 appears to disclose use at a surgical wound or site, and is focused on post surgical pain rather than chronic pain and acute or sub-chronic post-injury pain. Passage of active pharmaceutical agent is dependent on an anionic polymer carrier. There is nothing disclosing or suggesting focusing pharmaceutical effect at the locus of application. US 2004/0087520 appears to disclose delivery of therapeutic agents which depends on the compound lutrol in its various formulations. It lacks any capacity to easily cross the skin and localize to the site of action. US 2003/0161867; 2004/0126415; and 2004/0127531 appear to disclose a pharmacologic composition for application to an area of skin of a subject for local and / or systemic treatment of a COX-2 mediated disorder. They do not disclose or suggest a mixture of therapeutic agents to synergistically optimize the clinical effect, nor do they disclose or suggest the use of any specific ingredient to achieve and sustain localized effect. US 2004/0142911 appears to disclose a topical method for treating various forms of acute and chronic pain and its ingredients include at least one analgesic, namely, saliscyte. It is not clear how localized effects, if any, are achieved. US 2004/0151784 appears to disclose use of lactoferrin to reduce pain, alone, or in combination with other therapies for pain. Lactoferrin can

be administered orally, parenterally or topically. This patent, though presented as a treatment for pain, appears to depend on systemic, not localized effect. US 5,750,141 appears to suggest that a vasoactive agent, which may include phenylephrine, may be used to enhance the effect of another drug e.g. salicylate by modifying the vascular uptake of that drug from a site of active. However, there is no disclosure or suggestion of using a penetration-enhancer (solvent) in the manner disclosed by applicants. Further, the statement in column 5, lines 59-63 that "[t]he therapeutic agent(s) as described above are useful in treatment or having a therapeutic effect on tissues below the stratum corneum and thus cannot include substances which are primarily vehicles or carriers or solvents for a particular therapeutic agent . . ." actually excludes solvents and thus teaches directly away from applicants' disclosure of using a vasoconstrictor in combination with a penetration enhancer for topically delivering and localizing therapeutic agents. None of these patents or publications, separately or in combination, discloses, suggests or motivates applicants' disclosed and claimed combination of a vasoconstrictor for retarding vascular dispersion of a therapeutic agent; and a penetration enhancer for facilitating penetration of said vasoconstrictor and said therapeutic agent through a patient's skin.

Signature

Examiner Name	Date